



Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Disseminated *Mycobacterium avium* Complex Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.¹⁻³ *M. avium* is the etiologic agent in >95% of patients with AIDS who acquire disseminated MAC disease.^{1,4-9} An estimated 7% to 12% of adults have been previously infected with MAC, although rates of disease vary in different geographic locations.^{1,5,8,9} Although epidemiologic associations have been identified, no environmental exposure or behavior has been consistently linked to subsequent risk of developing MAC disease.

The mode of transmission is thought to be through inhalation, ingestion, or inoculation via the respiratory or gastrointestinal tract. Household or close contacts of those with MAC disease do not appear to be at increased risk of disease, and person-to-person transmission is unlikely.

MAC disease typically occurs in patients with CD4 T lymphocyte (CD4) cell counts <50 cells/mm³. The incidence of disseminated MAC disease is 20% to 40% in patients with severe AIDS-associated immunosuppression, in the absence of effective antiretroviral therapy (ART) or chemoprophylaxis.^{10,11} The overall incidence of disseminated MAC disease among HIV-infected patients has fallen more than 10-fold since the introduction of effective ART, to a current level of 2.5 cases of MAC as the first opportunistic infection (OI), per 1,000 person-years, for individuals in care.¹² Factors other than a CD4 count <50 cells/mm³ that are associated with increased susceptibility to MAC disease are high plasma HIV RNA levels (>100,000 copies/mL), previous OIs, previous colonization of the respiratory or gastrointestinal tract with MAC, and reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens, possibly reflecting defects in T-cell repertoire.

Clinical Manifestations

In patients with AIDS who are not on ART, MAC disease typically is a disseminated, multi-organ infection.¹³⁻¹⁷ Early symptoms may be minimal and can precede detectable mycobacteremia by several weeks. Symptoms include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.⁵

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase levels.^{1,2,4-11,18,19} Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) may be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities may occur with localized disease.

Localized manifestations of MAC disease have been reported most often in patients who are receiving and have responded to ART with an increase in CD4 T-cell counts, suggesting improved immune function. Localized syndromes include cervical or mesenteric lymphadenitis, pneumonitis, pericarditis, osteomyelitis, skin or soft-tissue abscesses, genital ulcers, or central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), described below.

Initially characterized by focal lymphadenitis with fever, IRIS subsequently has been recognized as a systemic inflammatory syndrome with signs and symptoms that are clinically indistinguishable from active MAC infection. Its occurrence with MAC disease is similar to IRIS or paradoxical reactions observed with tuberculosis (TB) disease.²⁰⁻²³ Bacteremia is absent. The syndrome has been described in patients with subclinical (unmasking IRIS) or established MAC disease and advanced immunosuppression who begin ART and have a rapid and marked increase in CD4 cell count (≥ 100 cells/mm³). As with TB, the syndrome may be benign and self-limited or may result in severe, unremitting symptoms that improve with the use of systemic anti-inflammatory therapy or corticosteroids in doses similar to those described for TB-associated IRIS.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph node, bone marrow, or other normally sterile tissue or body fluids.^{11,16,17,24,25} Species identification should be performed using specific DNA probes, high-performance liquid chromatography, or biochemical tests.

Other ancillary studies provide supportive diagnostic information, including acid-fast bacilli smear and culture of stool or tissue biopsy material, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

Preventing Exposure

MAC organisms commonly contaminate environmental sources, such as food and water. Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Indication for Primary Prophylaxis

HIV-infected adults and adolescents should receive chemoprophylaxis against disseminated MAC disease if they have CD4 counts <50 cells/mm³ (**AI**).

Preferred and Alternative Drugs for Prophylaxis

Azithromycin²⁶ and clarithromycin^{2,27} are the preferred prophylactic agents (**AI**). The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, associated with a higher rate of adverse effects than either drug alone, and **should not be used (AI)**.² The combination of azithromycin with rifabutin is more effective than azithromycin alone in preventing MAC disease.²⁶ However, based on the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared with azithromycin alone, this regimen **is not recommended (AI)**. Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. In patients who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC disease (**BI**), although drug interactions may complicate use of this agent. Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which for some patients may include obtaining a blood culture for MAC. TB also should be excluded before rifabutin is used for MAC prophylaxis because treatment with the drug could result in acquired resistance to *M. tuberculosis* in patients who have active TB.

Detection of MAC organisms in the respiratory or GI tract may predict disseminated MAC infection, but no data are available regarding efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs among asymptomatic patients harboring MAC organisms at these sites in the presence of a negative blood culture. Therefore, routine screening of respiratory or GI specimens for MAC **is not recommended**.

Discontinuing Primary Prophylaxis

Primary MAC prophylaxis should be discontinued in adults and adolescents who have responded to ART with an increase in CD4 count to >100 cells/mm³ for ≥ 3 months (**AI**). Two randomized, placebo-controlled trials and observational data have demonstrated that such patients can discontinue primary prophylaxis with minimal risk of acquiring MAC disease.²⁸⁻³² Discontinuing primary prophylaxis in patients who meet these criteria is recommended to reduce pill burden, potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. Primary prophylaxis should be reintroduced if the CD4 count decreases to <50 cells/mm³ (**AIII**).

Treating Disease

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance **(AI)**.^{3,8,9,33-40} Clarithromycin is the preferred first agent **(AI)**; it has been studied more extensively than azithromycin in patients with AIDS and appears to be associated with more rapid clearance of MAC from the blood.^{3,33,35,39-41} However, azithromycin can be substituted for clarithromycin when drug interactions or intolerance to clarithromycin preclude its use **(AII)**. Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.^{42,43}

Ethambutol is the recommended second drug **(AI)**. Some clinicians add rifabutin as a third drug **(CI)**. One randomized clinical trial demonstrated that adding rifabutin to the combination of clarithromycin and ethambutol improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance^{3,35} in individuals with AIDS and disseminated MAC disease. These studies were completed before the availability of effective ART. Whether similar results would be observed for patients receiving effective ART has not been established. The addition of a third or fourth drug should be considered in patients with advanced immunosuppression (CD4 count <50 cells/mm³), high mycobacterial loads (>2 log₁₀ colony-forming units/mL of blood), or in the absence of effective ART, settings in which mortality is increased and emergence of drug resistance is most likely **(CIII)**. On the basis of data in patients not infected with HIV, the third or fourth drug can include an injectable agent such as amikacin or streptomycin **(CIII)**, or possibly a fluoroquinolone such as levofloxacin or moxifloxacin **(CIII)**, both of which appear to have *in vitro* activity against MAC, although no randomized clinical trials have evaluated their singular efficacy in the setting of clarithromycin or azithromycin treatment or effective ART.⁴²

Special Considerations with Regard to Starting ART

ART generally should be started as soon as possible after the first 2 weeks of initiating antimycobacterial therapy in patients with disseminated MAC disease who have not been treated previously with or are not receiving effective ART **(CIII)**. The rationale for starting antimycobacterial therapy first is to lower the initial pill burden and to reduce the risk of drug interactions and complications associated with IRIS that might occur should both therapies be started simultaneously **(CIII)**. The rationale for starting ART as soon as possible after the first 2 weeks of antimycobacterial therapy is to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression **(CIII)**. If ART has already been instituted, it should be continued and optimized unless drug interactions preclude safe concomitant use of antiretroviral and antimycobacterial drugs **(CIII)**. Patients will need continuous antimycobacterial treatment unless they achieve immune reconstitution via antiretroviral drugs.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiating antimycobacterial therapy only in patients who fail to have a clinical response to their initial treatment regimens. Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 to 4 weeks after initiation of appropriate therapy; clinical response may be delayed, however, in those with more extensive disease or advanced immunosuppression.

Adverse effects with clarithromycin and azithromycin include nausea, vomiting, abdominal pain, abnormal taste, and elevations in liver transaminase levels or hypersensitivity reactions. Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI)**.⁴⁴ Rifabutin doses of ≥450 mg/day have been associated with higher risk of adverse drug interactions when used with clarithromycin or other drugs that inhibit cytochrome P450 (CYP450) isoenzyme 3A4 and may be associated with a higher risk of experiencing uveitis, arthralgias, neutropenia, or other adverse drug reactions.^{45,46}

Patients who develop moderate-to-severe symptoms typical of IRIS during ART should receive initial treatment with non-steroidal, anti-inflammatory drugs **(CIII)**. If IRIS symptoms do not improve, short-term

(4–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity **(CII)**.^{21,47}

Dosage adjustment with rifabutin is necessary in patients receiving protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) because of complex drug interactions.^{48,49} PIs can increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or PIs can be made on the basis of existing data. The ability of efavirenz to induce metabolism of clarithromycin can result in reduced serum concentration of clarithromycin but increased concentration of the 14-OH active metabolite of clarithromycin. Although the clinical significance of this interaction is unknown, the efficacy of clarithromycin for MAC prophylaxis could be reduced because of this interaction. Azithromycin metabolism is not affected by the CYP450 system; azithromycin can be used safely in the presence of PIs or NNRTIs without concerns about drug interactions.

Managing Treatment Failure

Treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia after 4 to 8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for patients whose disease relapses after an initial response. Most patients who experience failure of clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs at the time MAC disease was detected.^{3,8,9,33,50,51}

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multidrug regimen. The regimen should consist of at least two new drugs not used previously, to which the isolate is susceptible. Drugs from which to choose are ethambutol, rifabutin, amikacin, or a fluoroquinolone (moxifloxacin, ciprofloxacin, or levofloxacin), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling **(CII)**.^{8,9,34–38,41,52–56} Data in patients being treated for MAC who are HIV-uninfected indicate that an injectable agent such as amikacin or streptomycin should be considered **(CIII)**.⁴² Whether continuing clarithromycin or azithromycin despite resistance provides additional benefit is unknown. Clofazimine **should not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality **(AI)**.^{34,36,54} Anecdotal evidence exists for use of other second-line agents, such as ethionamide, thiacetazone (which is not available in the United States) and cycloserine in combination with clarithromycin and azithromycin as salvage therapy, but their role in this setting is not well defined. Optimization of ART is an important adjunct to second-line or salvage therapy for MAC disease in patients for whom initial treatment is unsuccessful or who have disease that is resistant to antimycobacterial drugs **(AIII)**.

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for routine use.

Preventing Recurrence

When to Start Secondary Prophylaxis

Adult and adolescent patients with disseminated MAC disease should continue secondary prophylaxis (chronic maintenance therapy) **(AII)** unless immune reconstitution occurs as a result of ART.^{29,30}

When to Stop Secondary Prophylaxis

Patients are at low risk of recurrence of MAC when they have completed a course of ≥ 12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have an increase in their CD4 counts to >100 cells/mm³ that is sustained for >6 months after ART. It is reasonable to discontinue maintenance therapy in these patients, given experience with patients who have been evaluated and inferences from more extensive data that indicate the safety of discontinuing secondary prophylaxis for other OIs **(AI)**.^{30,38,57,58} Secondary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm³ **(AIII)**.

Special Considerations During Pregnancy

Chemoprophylaxis for MAC disease in pregnant women and adolescents is the same as for those who are not pregnant (**AIII**). Because clarithromycin is associated with an increased risk of birth defects evident in certain animal studies, it **is not recommended** as the first-line agent for prophylaxis or treatment of MAC in pregnancy (**BIII**). Two studies, each with slightly more than 100 women with first-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk of spontaneous abortion was noted in one study.^{59,60} Azithromycin did not produce defects in animal studies, but experience is limited with use in humans during the first trimester. Azithromycin is recommended for primary prophylaxis in pregnancy (**BIII**). For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination (**BIII**).

Diagnostic considerations and indications for treatment of pregnant women are the same as for women who are not pregnant. On the basis of animal data discussed previously, azithromycin is preferred over clarithromycin as the second agent to be combined with ethambutol for treatment of MAC disease (**BIII**). Use of ethambutol should minimize concerns regarding drug interactions, allowing initiation of ART as soon as possible during pregnancy to decrease the risk of perinatal transmission of HIV. Pregnant women whose disease fails to respond to a primary regimen should be managed in consultation with infectious disease and obstetrical specialists.

Recommendations for Preventing and Treating Disseminated *Mycobacterium avium* Complex (MAC) Disease (page 1 of 2)

Preventing 1st Episode of Disseminated MAC Disease (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- CD4 count <50 cells/mm³ after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some patients) (**AI**)

Preferred Therapy:

- Azithromycin 1200 mg PO once weekly (**AI**), *or*
- Clarithromycin 500 mg PO BID (**AI**), *or*
- Azithromycin 600 mg PO twice weekly (**BIII**)

Alternative Therapy:

- Rifabutin 300 mg PO daily (**BI**) (dosage adjusted may be necessary based on drug-drug interactions, please refer to [Table 5](#) for dosing recommendation when used with ARV drugs).

Note: Active TB should be ruled out before starting rifabutin.

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >100 cells/mm³ for ≥3 months in response to ART (**AI**)

Indication for Restarting Primary Prophylaxis:

- CD4 count <50 cells/mm³ (**AIII**)

Treating Disseminated MAC Disease

Preferred Therapy:

At least 2 drugs as initial therapy to prevent or delay emergence of resistance (**AI**)

- Clarithromycin 500 mg PO twice daily (**AI**) + ethambutol 15 mg/kg PO daily (**AI**), *or*
- Azithromycin 500–600 mg (**AII**) + ethambutol 15 mg/kg PO daily (**AI**) when drug interactions or intolerance precludes the use of clarithromycin

Note: Testing of susceptibility to clarithromycin or azithromycin is recommended.

Recommendations for Preventing and Treating Disseminated *Mycobacterium avium* Complex (MAC) Disease (page 2 of 2)

Alternative Therapy:

Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4 count <50 cells/mm³), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART (**CIII**).

The 3rd or 4th drug options may include:

- Rifabutin 300 mg PO daily (**CI**) (dosage adjusted may be necessary based on drug-drug interactions), *or*
- An aminoglycoside (**CIII**) such as amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily, *or*
- A fluoroquinolone (**CIII**) such as levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Same as treatment regimens

Criteria for Discontinuing Chronic Maintenance Therapy (AII):

- Completed at least 12 months therapy, *and*
- No signs and symptoms of MAC disease, *and*
- Have sustained (>6 months) CD4+ count >100 cells/mm³ in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 <100 cells/mm³ (**AIII**)

Other Considerations:

- NSAIDs may be used for patients who experience moderate to severe symptoms attributed to IRIS (**CIII**).
- If IRIS symptoms persist, a short term (4–8 weeks) of systemic corticosteroid (equivalent to 20–40 mg of prednisone) can be used (**CII**).

Key to Acronyms: MAC = *Mycobacterium avium* Complex; CD4 = CD4 T lymphocyte; PO = orally; BID = twice daily; ARV = antiretroviral; TB = tuberculosis; CFU = colony-forming units; ART = antiretroviral therapy; IV = intravenous; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; NSAIDs = Non-steroidal anti-inflammatory drugs

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